K4

37. (Amended) The method of claim 35 wherein said disease is multiple sclerosis and said autoantigen is bovine myelin basic protein.

38. (Unchanged) The method of claim 29 wherein said autoantigen is contained in tissue that is the site of attack in the autoimmune disease.

40. (Unchanged) The method of claim 35 wherein said autoantigen is contained in tissue that is the site of attack in the autoimmune disease.

REMARKS

This submission is in response to the Official Action dated March 19, 2002. Claims 29-41 were pending claims. Claims 30, 34, 36, 39 and 41 have been canceled either to avoid the double patenting rejection (claims 34, 36) or redundancy (claims 39, 41). Claims 29, 35 and 37 have been amended to make even more clear that the present claims are directed to suppression of an autoimmune response, and not to a "cure," (Claims 29 and 35), and to correct the scope of claim 37. Reconsideration of the above identified application, in view of the above amendments and the following remarks, is respectfully requested.

Alleged Drawing Corrections

It is believed that inclusion of Paragraph 6 in the Office Action was in error since no drawing changes were required in the Action, and no draftsman's PTO 948 accompanied the Office Action. Nevertheless, in an attempt to be responsive, applicants provide herein a set of formal drawings with identifying indicia in the back.

Rejection of Claims 31, 38 and 40 For Lack of Support

Support for bovine myelin basic protein can be found in Example 6, p. 21, lines 9-13. Support for "tissue that is the site of attack" in claims 38 and 40 can be found in the detailed description, p. 7, lines 2-3 as part of the definition of "autoantigen" where the specification clearly states, "[s]uch compounds may consist of tissue from a target organ that is the site of attack in an autoimmune disease." Accordingly, the rejection of claims 31, 38, and 40 for lack of support has been addressed and is believed to have been overcome.

Rejection of Claims 29-41 For Lack of Enablement

The present claims are clearly limited to (i) treatment by suppression of an autoimmune response; and (ii) autoimmune responses associated with T-cell mediated or T-cell dependent autoimmune diseases. Therefore, the present claims clearly exclude poison ivy and do not require a cure or even an improvement of such clinical parameters as are measured in a Phase III clinical study. Instead, the present

claims require abatement of an abnormal autoimmune response, which was not measured in either of the Phase III clinical trials referred to by the Examiner. The undersigned has studied the protocol for both clinical studies. The parameters measured were:

- Annual Attack Rate (primary parameter);
- Total brain hemispheric lession volume;
- Expanded Disability Status Scale;
- Attack frequency;
- Time to first attack;
- Proportion of attack-free patients;
- Frequency of steroid use; and
- Clinicians's global evaluation score. (Tab 1).

The only human study in which autoimmunity was measured was the one reported in Science [Tab 2: Weiner et al., Science 1993, 259: 1321-1324; courtesy copy attached], of record, in which activated T-cells were found to be reduced in a majority of patients in the study. See Table 4, p. 1323 of the Science paper.

Based on the failure of the clinical studies, which did not measure T-cell activation or number or autoimmune response, the Examiner has concluded that the claimed method is unpredictable and that the present claims should be limited to the animal models specifically exemplified: EAE and adjuvant arthritis. This rejection is

respectfully traversed for the reason set forth above: the clinical studies on which the Examiner relies did not measure autoimmune response. Moreover, it is well-known that clinical studies fail for many reasons unrelated to the operability of an invention: there may be an inadequate number of study participants (Tab 3: Waagstein et al., Lancet 1993, 342:1441-1446, at 1445); inadequate study duration (Tab 4: Muth et al., Control Clin. Trials 2001, 22(1):49-55; Tab 5 Medical Industry Today, Jan. 28, 1997); variability in the administration of a biologic, (Tab 6: Women's Health Weekly, July 21, 2001, pp. 17-18); and hyperplacebo effects (Tab 6: Women's Health Weekly, July 21, 2001, pp. 17-18) (courtesy copies of articles enclosed). Hence, the clinical studies provide no evidence that the claimed method is inoperative.

The Examiner has also based this rejection on stock recitation of unpredictability of all physiological processes in MPEP § 2164.03 as well as on a recitation of the In re Wands factors. However, these factors are a mere abstraction unless supported by the clinical studies, which as shown above, the Examiner should not rely on.

Thus, absent the Phase III clinical studies, the invention has been demonstrated in two very different experimental systems. The only thing they have in common is that they model two entirely different T-cell mediated autoimmune

diseases. Cohen et al. (cited in the previous response) have shown that the family of such diseases is due to a harmful T-cell. Therefore the extrapolation is warranted.

The Examiner has also dismissed the applicants' discussion of what the experiments described in the Examples of the specification conveyed to a person of ordinary skill in the art at the time, and what these experiments were designed to demonstrate by those who designed them at the time, and what these experiments were designed to demonstrate by those who designed them at the time. These experiments were designed for publication in peer reviewed journals and hence to be read and interpreted by those of ordinary skill in the art at the time. There is no ex post facto fabrication of a mechanism or methodology here. Cohen et al. had shown that all of these diseases were perpetrated by harmful T-cells activated against the tissue under attack. Others had shown that this was true in the human disease as well. The experiments in the specification show that these T-cells can be neutralized by feeding not only the antigen that theseT-cells recognized, but also an antigen that was from the same tissue that they did not recognize. By "Example 4" in the last Amendment, Applicants meant to refer to Table II, p. 18 of the Specification. Therein, suppression is shown even after immunization. Example 10 relates to adoptive transfer of protection which would not have occurred if the mechanism had not been active suppression.

The only possible conclusion from these experiments is that there is active suppression at work in abating the harmful autoimmune-like response. This means that the claimed method has applicability beyond the particular experiment and beyond the particular disease model.

Taken together, (a) Cohen's findings of a common mechanism of autoimmunity in T-cell mediated (or dependent) autoimmune diseases; (b) the findings that humans suffering from these diseases have activated T-cells directed against the target organ or tissue; (c) applicants' findings that an autoimmune response can be abated by oral tolerance in disparate disease models (but always in models of T-cell mediated (or dependent) autoimmune disease); (d) that oral tolerance can be induced by another antigen, not necessarily the one used to induce disease (See pp. 34-35); and (e) that oral tolerance can be adoptively transferred (Example 10), accomplish the following:

- they preclude anergy as a means of achieving oral tolerance;
- they support an active mechanism of suppression; and
- they validate the method for other T-cell mediated (or dependent) autoimmune diseases.

Therefore, in view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,

Sandra Lee

Sandra S. Lee (Reg. 51,932) for
Adda C. Gogoris
Reg. No. 29,714
Attorney for Applicants

DARBY & DARBY, P.C.
Post Office Box 5257
New York, NY 10150-5257
Phone (212) 527-7700

EXPRESS MAIL CERTIFICATE

Date 9/19/02 Label No. EV 181599305

I hereby certify that, on the date indicated above, this paper or fee was deposited with the U.S. Postal Service & that it was addressed for delivery to the Assistant Commissioner for Patents, Washington, DC 20231 by "Express Mail Post Office to Addressee" service.

Pat Campbell
Name (Print)

Signature

PLEASE CHARGE ANY DEFICIENCY OR CREDIT ANY EXCESS IN THE FEES DUE WITH THIS DOCUMENT TO OUR DEPOSIT ACCOUNT NO. 04-0100

Customer No.: 07278
PATENT TRADEMARK OFFICE

Docket No: 1010/16104-US4

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Howard L. Weiner et. Al.

Serial No.: 08/279,275 Art Unit: 1644

Confirmation No.: 7626

Filed: July 22, 1994 Examiner: Ewoldt, Gerald R.

For: TREATMENT OF AUTOIMMUNE DISEASES BY ORAL ADMINISTRATION OF AUTOANTIGENS

MARK-UP AMENDMENT PURSUANT TO 37 C.F.R. § 1.121

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

September 19, 2002

Sir:

In response to the Official Action dated March 19, 2002, please amend the above-identified application as follows:

IN THE SPECIFICATION:

Please delete the first paragraph of the application following the title on page 1 lines 13-16, and replace it with the following:

This application claims priority to U.S. Patent Applications Serial No. 07/460,852 filed February 21, 1990 and 07/065,734 filed June 24, 1987, both abandoned.

IN THE CLAIMS:

Please amend the claims pursuant to 37 C.F.R. 1.121 as follows (see the accompanying "marked up" version pursuant to 1.121):

Please cancel claims 30, 34, 36, 39 and 41 amend the remaining claims as follows:

29. (Amended) A method for the treatment of a T cell-mediated or T cell-dependent autoimmune disease by suppressing an autoimmune response associated with said disease in a human [suffering from] presenting with said autoimmune [disease] response, said method comprising orally or enterally administering to said human at least one antigen in an amount effective to suppress

said autoimmune response, said antigen selected from the group consisting of autoantigens specific for said autoimmune disease, said suppression comprising elicitation of suppressor T cells specific to said administered antigen.

31. (Unchanged) The method of claim 29 wherein said autoantigen is administered orally.

32. (Unchanged) The method of claim 29 wherein said autoantigen is administered enterally.

33. (Unchanged) The method of claim 29 wherein said autoimmune disease is multiple sclerosis.

35. (Amended) A method of treating a T cell-mediated or T cell-dependent autoimmune disease by suppressing an autoimmune response associated with said disease in a human [suffering from] presenting with said autoimmune [disease] response, said method comprising orally or enterally administering to said human at least one antigen in an amount effective to suppress said autoimmune response, said antigen selected from the group consisting of autoantigens specific for said autoimmune disease.

37. (Amended) The method of claim 35 wherein said disease is multiple sclerosis and said autoantigen is bovine myelin basic protein.

38. (Unchanged) The method of claim 29 wherein said autoantigen is contained in tissue that is the site of attack in the autoimmune disease.

40. (Unchanged) The method of claim 35 wherein said autoantigen is contained in tissue that is the site of attack in the autoimmune disease.